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DRUG ALLERGY

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For thousands of years, people have been treating their illnesses with various drugs. At first these were natural substances such as herbs and the juices or saps from plants that were eaten or applied to the skin. Doctors still use some of these natural products—for example, quinine obtained from the bark of the cinchona tree and digitalis prepared from the dried leaf of the foxglove plant. Today, however, most drugs available to the doctor are man-made chemicals designed to combat specific diseases or sets of symptoms.

As more drugs become available and are used, the number of adverse reactions to them increases. The World Health Organization's definition of an "adverse drug reaction" is any response to a drug that is harmful and not intended and that occurs at doses given to individuals for prevention, diagnosis, or treatment of disease.

One of the major public health problems today is drug-induced illness. Between 3 and 5 percent of medical hospital admissions are due to adverse drug effects, and 10 to 20 percent of patients hospitalized for other reasons have an adverse response to a drug prescribed while they are hospitalized. The Department of Health and Human Services has estimated that the annual cost of *treating* adverse drug reactions in U.S. hospitals is approximately $3 billion. Thus, in addition to the individual suffering and even death in rare cases, adverse drug reactions have become a costly problem indeed. Some of these adverse reactions to drugs are recognized as allergies.

WHAT IS AN ALLERGY?

An exaggerated sensitivity to a substance that causes no problem for most people is termed an "allergy" when it involves the body's immune system. Many substances can cause an allergic reaction. The most common ones are airborne pollens, molds, house dust, and animal danders; certain foods; insect venoms; and drugs. The symptoms may be mild, such as a stuffy nose or tearing eyes, or they may be generalized, severe, and even life-threatening, such as vascular collapse (anaphylactic shock) and airway obstruction.

One can encounter an allergy-provoking substance by several routes including inhalation, injection, ingestion, and skin contact. When an allergy-prone person is first exposed to such substances by any of these routes, the immune system, which is the body's defense mechanism against foreign invaders, responds in a number of ways.

One type of allergic reaction involves the immune mechanism that stimulates specialized kinds of white blood cells called lymphocytes to mature into plasma cells. It is these plasma cells that make immunoglobulin antibodies in response to their first exposure to foreign invaders (called antigens), such as viruses, bacteria, pollens, and some drugs. Usually, immunoglobulins have a protective role. However, in this case immunoglobulins of the IgE class are produced, which can "sensitize" or "prime" the affected person for a future allergic response.

Many kinds of antibodies protect the body by helping to fight off and destroy bacteria and viruses. Yet IgE antibodies, which are responsible for most allergies, have other properties that are often harmful to the

allergic patient. These IgE antibodies in allergy-prone people attach themselves to certain cells in the body known as mast cells and basophils. Mast cells are found in body tissues, especially the respiratory and digestive tracts and in the skin; basophils are found in the blood.

The next time that a sensitized person encounters the specific foreign antigen, the IgE antibodies are lying in wait for it on the surfaces of the mast cells and basophils. These antigens bind to their corresponding IgE antibodies, causing the mast cells and basophils to release into the surrounding tissue certain irritating chemicals that produce the symptoms of allergy, such as sneezing, watery eyes, hives, abdominal pain, diarrhea, and skin rashes. One of these chemicals is histamine, a name familiar to many allergy sufferers. It brings on allergies by producing inflammation, which results from expansion of blood vessels and leakage of fluids through the stretched walls. A massive activation of the IgE system results in severe symptoms and possibly even fatal shock.

Interestingly, each antibody will react only to the specific antigen against which it was made. For example, an IgE antibody that is produced by plasma cells against house dust will not react to ragweed pollen. Thus a person who is allergic only to house dust will not have allergic symptoms when exposed to ragweed pollen. Similarly, a person allergic only to ragweed pollen will not have allergic symptoms when exposed to house dust.

This IgE antibody-antigen reaction is only one way that the body's immune system deals with foreign invaders. In another type of allergic response, antibodies of the IgG class are produced, enter the circulation, and attach to the surfaces of and destroy cells containing the corresponding antigen.

Such an event results from a transfusion in which mismatched blood is used. This type of reaction may also occur in unusual instances when a person's own blood cells become the target of attack by IgG if the cells are made to appear foreign by being coated with a drug. Such red blood cell destruction can lead to a drug-induced anemia.

These first two types of allergic reactions can occur quickly. A third type of reaction occurs several hours or days after exposure to an antigen and results when other types of harmful IgG antibodies and antigen combine into complexes which are then deposited in the walls of blood vessels, in the skin, or in the kidneys. Horse serum, formerly used in immunization injections against tetanus, was a common cause of this type of allergic reaction, called serum sickness. Some allergic reactions to penicillin are caused by an identical mechanism.

The allergic response known as "delayed hypersensitivity" reaches its peak 2 or 3 days after exposure of an allergic person to the offending antigen. This response is also known as "cell-mediated" immunity because certain kinds of sensitized lymphocytes themselves (rather than their antibody products) bring about the inflammatory reaction. Classic examples of this reaction are the skin test for tubercle bacilli (TB) and skin rashes caused by poison ivy. Only after 24 hours or more does the skin show a response to the test.

What is drug allergy?

When the body's immune system reacts against a drug, the adverse response that may sometimes result is known as an "allergic reaction." General reactions such as

anaphylaxis, serum sickness, and asthma are typical of the unusual responses of the body's immune system to antigens; thus the occurrence of these symptoms in an adverse drug reaction is indicative of an allergic response. Other reactions to drugs are classified as allergic only on the basis of their clinical features and response to treatment. Because it is often very difficult to diagnose positively an allergy to a drug, the exact number of such reactions that occur each year cannot be counted.

How does drug allergy develop?

There are three steps in the development of drug allergy. First, a susceptible person must be *exposed* to the drug. Next, the body's immune system must be made *allergic* to the drug by the build-up of sensitized lymphocytes or antibodies produced by plasma cells. Third, the person must be *reexposed* to the same drug. Usually only after this second or later exposure will the symptoms of the allergy appear. Allergic responses to drugs differ widely, but a person's own pattern of reaction to a particular drug generally does not vary. However, some people will occasionally tolerate a certain drug for months or even years, then they will suddenly suffer a severe allergic reaction to it. After that, even a tiny amount of the drug will cause symptoms.

The response of the body to a drug depends on such factors as the dosage, frequency and route of administration of the drug, and a person's own makeup. For example, intermittent (on-and-off) doses of a drug are more likely to lead to an allergic reaction than is long continuous use. Usually, most drugs are less likely to lead to an allergic reaction if given by mouth than by injection. A

number of drugs (e.g., antihistamines) applied directly to the skin may sensitize, but they will have less allergic effect when given by injection or by mouth.

Generally, whether a person is a male or a female makes little difference in drug reactions. Age, however, is important. Children and elderly people are less likely than others to have drug reactions. This is perhaps because the immune system is immature in babies and tends to be less reactive in the elderly. It is unclear whether a person who is allergic to one drug is predisposed to allergic reactions to a new drug. Certainly, one should avoid further exposure to drugs having the same chemical makeup as the drug that first provoked the allergic response. Exposure to the sun sometimes increases the chance of an allergic reaction to certain drugs applied to the skin and even to some taken by mouth. When the intestines, kidneys, or liver are damaged and malfunction, the risk of allergy is greater because of the resulting inability of these organs to metabolize and excrete drugs.

The breakdown products of a drug that are formed as the body uses the drug occasionally may be the culprits rather than the drug itself in causing the reaction. In some cases, the body's allergic response is caused not by the drug or its breakdown products but by other chemicals added to the drug to preserve it (e.g., benzoic acid, methylparabens) or to improve its flavor or odor (e.g., terpenes).

Which drug reactions are nonallergic?

More than half of the adverse drug reactions reported by doctors are not allergic by definition. Such reactions may be classified as overdosage, idiosyncrasy, side effects,

paradoxical response, or drug interactions. All drugs, even over-the-counter ones, can cause these responses. Great variations occur in the symptoms, their frequency, and their severity among different patients.

Symptoms of overdosage may obviously result from too large an amount of medication taken. For example, an overdose of aspirin may cause a "ringing" in the ears. Yet overdosage may also be caused by the unexpected accumulation of a drug in a patient whose impaired or inadequate body function is unable to break it down or excrete it at a normal rate.

Many abnormal or unexpected reactions to drugs are termed "idiosyncratic." Examples include an unexpected response to an ordinary dose of a drug (e.g., reduced production of blood cells with use of the antibiotic chloramphenicol); a toxic response to a low dose of a drug (e.g., "ringing" in the ears with use of quinine, sometimes prescribed to relieve muscle cramps); or an unusual resistance to a large dose of a drug. Some idiosyncratic reactions are now known to have a genetic basis.

Side effects of drugs—undesirable yet unavoidable actions of medications and not related to the desired effect—are frequently encountered. Sleepiness after taking antihistamines and diarrhea that sometimes accompanies use of antibiotics are common examples. Patients may sometimes find it necessary to tolerate annoying yet harmless side effects of a medication in order to experience its curing effects.

Paradoxical responses are ones that vary from the reactions usually expected after a drug is administered and result in the opposite effect. One example is a case of the "jitters" after taking a sedative.

The interaction of one or more drugs being taken by a patient at the same time may

also cause adverse reactions. These interactions occur when one drug alters the body's ability to use another drug or when a combination of two or more drugs modifies the effects of each drug. The interaction of two common drugs—alcohol and tranquilizers—can cause reactions that range from drowsiness to death.

Thus it is probable that a person may experience an adverse reaction to a drug without being allergic to it. The symptoms of nonallergic and allergic reactions to medication are sometimes very similar.

What are the symptoms of drug allergy?

Because drugs may affect several organs in the body, it is sometimes hard to decide whether a patient's symptoms result from the illness itself or from an allergic reaction to a drug. For example, a rash may appear during or after some streptococcal infections. Yet a rash may also be a symptom of an allergy to penicillin, an antibiotic used to treat the same streptococcal infections.

The symptoms that will appear in those who develop allergic reactions to drugs are impossible to predict ahead of time. A drug allergy may affect a single organ and a localized area of the body or it may affect many organs and many sites at the same time. Reactions on the skin are obvious and common. Reactions in other parts of the body may be difficult to detect; these are probably more frequent than people may think. The most common allergic responses of various parts of the body are reviewed here.

Skin reactions.—An estimated 15 percent of all visits to dermatologists are concerned with adverse reactions to drugs. In fact, skin reactions are the most common symptoms

of drug allergy and include hives, several other types of rashes, and itching. These symptoms may occur anywhere on the body and result from drugs taken by mouth or injection or from direct contact with a drug applied to the skin. Exfoliative dermatitis is an especially severe allergic reaction in which much of the skin of the body becomes red and peels off.

Contact dermatitis, which produces swelling, reddening, itching, or eruptions on the skin at the site of contact with a drug, often develops in nurses or druggists who handle drugs. Patients may also develop contact dermatitis from medications applied directly to the skin. Allergic reactions may be provoked by soap and antibiotic creams as well as by local anesthetics used to numb pain. Examples are procaine (Novocain), which dulls the pain of dental work, and many over-the-counter sprays containing benzocaine that are applied to the skin to numb the pain of sunburn, minor cuts, and insect bites.

Symptoms of contact dermatitis may appear within several hours or as long as 48 hours after the medicine is applied to the skin. If the person stops using the offending drug promptly, the reaction usually will end in a few days.

Another type of drug allergy that affects the skin is a "photosensitivity" reaction. Reddenings and eruptions appear on areas of the skin exposed to sunlight after a person has taken a sensitizing drug by mouth or injection or has applied it to the skin. For example, some people who venture out into the sun after taking griseofulvin (an antifungal agent), sulfa drugs and tetracyclines (antibiotics), chlordiazepoxide (a sedative), or thiazides (diuretics) may get a rash that looks like a sunburn.

Lung reactions.—The lung is involved in a

number of allergic reactions to drugs. Certain drugs may cause a sudden onset of bronchial asthma; other drugs such as para-aminosalicylic acid (used to treat TB), sulfa drugs, and penicillin may induce pneumonia. Still others such as hydralazine (used to lower blood pressure) produce symptoms that mimic a disease known as lupus by causing inflammation of the membrane (pleura) that lines the lung. Usually damage to the lungs is not permanent, and after treatment is stopped the lung function becomes normal.

Reactions of other organs.—Sometimes portions of the liver, kidneys, and blood vessels will become inflamed in response to long-term or high-dose treatment with drugs. These allergic reactions (hepatitis, nephritis, and vasculitis) usually take weeks or months to develop. If the offending drug is discontinued when the symptoms first appear, the harmful effects may be reversed. Continued use of the drug may cause the symptoms to persist or get worse.

Certain drugs may cause an allergic reaction in which large numbers of red blood cells are destroyed; this condition is known as hemolytic anemia. Other drugs may attack blood platelets, which promote clot formation, and abnormal bleeding may result; still others may attack a type of white blood cells called granulocytes, which are active in fighting germs, and resistance to infection may be impaired.

General systemic reactions.—Such reactions as drug fever, serum sickness, angioedema, and anaphylactic shock affect many different tissues of the body. Drug fever generally will appear about a week after medication has been started. Such a fever will often subside within a day or two after the drug is withdrawn. Sometimes drug-induced fevers are not diagnosed because it is difficult to decide whether the

fever is caused by the disease or by an allergic reaction to the drug being used.

Serum sickness occurs when animal serum must be injected into humans. However, conditions similar to serum sickness may also be noted after continual use of certain drugs such as penicillin, sulfa compounds, and phenytoin (an anticonvulsant). An allergic patient will develop a fever, rash, hives, swollen lymph glands, facial swelling, and painful joints. These symptoms depend on antibody formation and thus appear as early as 10 days after the first dose or 2 to 3 weeks after the last dose, but they will subside after the serum or drug and its antibodies have been cleared from the body.

Angioedema or giant hives is the sudden appearance of massive swollen areas of the skin, mucous membranes, and occasionally, internal organs. Angioedema in the throat causes the airway to become blocked and makes breathing difficult. Such cases may be life-threatening and need emergency medical treatment. The symptoms of swelling in areas other than the throat may be unpleasant but are not usually life-threatening.

Anaphylactic shock is less common than other allergic reactions to drugs. Often severe anaphylactic shock is preceded by the sudden onset of violent itching, especially on the soles of the feet and palms of the hands, and by reddening of the skin as if it were sunburned, particularly around the ears. Hives may occur, and the face may become distorted with swelling. The patient may suddenly have trouble breathing and may feel faint and anxious. The blood pressure becomes dangerously low. Convulsions, shock, and unconsciousness may occur, and occasionally the outcome may be fatal.

The typical anaphylactic reaction to drugs develops rapidly and becomes most severe

within 5 to 30 minutes. The symptoms can usually be reversed if epinephrine (Adrenalin) is given quickly; however, emergency medical treatment is essential for a severe reaction.

which drugs are the major culprits?

Antibiotics.—The numbers of antibiotics available today that may cause allergic reactions are too numerous to record here. This section deals with only a few.

Penicillin is probably the most common cause of drug allergy, with some type of allergic response occurring in one of every 50 persons who take this antibiotic. About 76 percent of these responses are skin reactions (hives, rashes, contact dermatitis) and about 22 percent are systemic (serum sickness, drug fever, vasculitis, angioedema, wheezing); only 2 percent of the reactions to penicillin involve anaphylactic shock.

Neomycin, an antibiotic that may be an ingredient of eye drops, often causes allergic contact conjunctivitis (pink eye). As an ingredient of ointments, neomycin may produce symptoms similar to allergic contact dermatitis.

Allergic responses to streptomycin may range from mild reactions of the skin to drug fever and even to anaphylactic shock.

Chloramphenicol, used in the treatment of Rocky Mountain spotted fever, typhoid fever, and certain types of meningitis, may affect the production of blood cells. An especially severe reaction to this antibiotic is aplastic anemia, a blood disorder in which the body's bone marrow fails to produce enough blood cells.

The new sulfonamides (sulfa drugs) now on the market produce fewer allergic reactions than did the sulfa compounds produced

many years ago. However, the long-acting sulfa drugs may cause allergic responses such as hives, angioedema, skin rashes, fever, blood disorders, hepatitis, inflammation of the lungs and blood vessels, or a form of pneumonia. Included in this category of long-acting sulfas are those used as diuretics (drugs to counter fluid retention) as well as antibiotics.

Insulin.—Allergic reactions to insulin are common. The symptoms range from pain and swelling at the site of injection to hives all over the body and severe reactions such as shock.

Insulin is prepared from both pork and beef pancreas, and because it is an animal protein, it can cause allergic reactions. The main factors that appear to be related to insulin allergy are the type of insulin used when treatment is begun and the genetic makeup of the patient. Most patients with insulin allergy have only delayed local reactions at the injection site; these last just a short time, and the patients are able to continue treatment without further problems. (Whether these are truly allergic responses is questionable.)

Although most insulin reactions are due to the hormone itself or to the animal protein, other reactions are due to incidental components. For example, some of the allergic skin reactions to insulin are now thought to be caused by zinc, which is used in commercial preparations of insulin. Zinc-free insulin, which is now available, has not produced any allergic responses in zinc-sensitive people.

Other drugs.—Some of the common drugs that may also cause allergic reactions include antituberculosis medications and other antibiotics not discussed above, anticonvulsants, barbiturates, local anesthetics, heavy metals, organ extracts, vaccines, tranquilizers and sleeping pills, laxatives,

and drugs used to treat hyperthyroidism and heart disorders.

Which drugs provoke pseudoallergic responses?

Some reactions to drugs have all the symptoms of an allergic response. However, laboratory tests have failed to show evidence that the body's immune system is involved, so these reactions are termed "pseudoallergic." The most common symptoms are hives and/or angioedema, skin rashes, spasms of the airway passages, and shock.

Among the drugs known to induce pseudoallergic reactions are aspirin, tartrazine (yellow food dye No. 5), contrast dyes used in some X-ray studies, and ampicillin.

Aspirin.—About one million Americans have pseudoallergic reactions to aspirin. Although many otherwise nonallergic people (nearly 1 percent) react to aspirin, persons who have allergy-related problems are more susceptible to this condition. For example, a recent report by a task force of the National Institute of Allergy and Infectious Diseases (NIAID) revealed that those who suffer from chronic hives, asthma, and/or hay fever are more likely to have adverse reactions to aspirin than are those without these conditions.

Aspirin is an ingredient of many over-the-counter drugs, such as headache remedies, pain-killers, and cold medicines. It has also been found that people who have pseudoallergic reactions to aspirin may also have the same response to other drugs such as arthritis remedies (indomethacin, phenylbutazone).

Tartrazine (yellow food dye No. 5).—Between 15 and 25 percent of Americans

with an intolerance to aspirin may also react adversely to this dye. However, pseudo-allergic responses to tartrazine can occur in people who have no intolerance to aspirin. Tartrazine is common in many artificially colored foods, candies, and beverages; in the yellow coatings on some prescription pills (even some pills prescribed for asthma); and in liquid medicine colored yellow.

Contrast dyes.—Sometimes dyes that contain organic iodine are injected into a patient's blood vessels during special kinds of X-ray tests. These dyes are used because they help to outline specific organs (e.g., kidneys, heart, blood vessels, gallbladder) in the X-ray picture. In about 3 percent of patients, injections of these dyes cause reactions such as hives, itching, rashes, angioedema, asthmatic attacks, or even shock.

Ampicillin.—This frequently prescribed antibiotic may cause a nonallergic skin rash that may be mistaken for allergic dermatitis. The rash occurs in about 9 percent of people treated with ampicillin and in as many as half of the patients with infectious mononucleosis who take the drug.

How is drug allergy diagnosed?

The diagnosis of drug allergy is usually made on the basis of the patient's medical history. Often the patient is the one who first notices the symptoms. Skin rashes, hives, swelling, fever, cough, and asthma may be signs of an allergic reaction to a drug and should be reported to the doctor, even if the reaction is slight. The doctor relies strongly on information that the patient supplies about the drug taken—when, how much, the length of time before symptoms appear, and what other medicine is being taken at the same time. Too often pa-

tients fail to report use of laxatives, nose drops, tonics, cold and cough remedies, antihistamines, vitamins, ointments, birth control pills and creams, douches, suppositories, aspirin and other pain killers, headache remedies, and antacids because they do not consider these compounds to be "drugs."

If the doctor suspects that an allergic reaction to a drug has occurred and if the symptoms generally begin to subside within 24 to 48 hours after the drug has been removed, it is likely that the drug has indeed caused the reaction. Occasionally, however, especially severe symptoms may continue or become worse for a week after a drug is stopped. A long-lasting drug may even cause allergic reactions for weeks or months after a patient has stopped taking it.

Depending on the patient's symptoms and the length of time before they subside, the doctor may again prescribe small amounts of the same medication to confirm the diagnosis. Such a rechallenge can be very dangerous, especially if the patient has had a previous life-threatening allergic reaction. The doctor's decision to reuse the drug must be based on the need to know whether the patient has a drug allergy, the severity of the allergic reaction, the seriousness of the disease, and the availability of acceptable drug substitutes.

Although skin tests are used to detect allergies to pollens, molds, dust, animal danders, and food substances, most attempts to diagnose sensitivity to a drug by using the drug itself for skin testing are usually unsuccessful. This is because the exact derivative or breakdown product of the drug that acts as the antigen is not known. The patch test, if applied carefully, may help to diagnose contact dermatitis caused by drugs or chemicals. However, useful diag-

nostic tests generally do not exist to tell whether a drug reaction was allergic, which drug caused it, or whether a patient will suffer an allergic response to a drug that the doctor wants to prescribe.

Thus the diagnosis of drug allergy at present relies heavily on circumstantial evidence—the medical history, present symptoms, and time lapse between use of the drug and appearance of the symptoms. Careful diagnosis is important because it may affect not only the person's current therapy but also medication in the future.

How is drug allergy treated?

Like other allergies, no simple cure exists for drug allergy. Sometimes it disappears by itself within a matter of months or years.

The first step in treating drug allergy is identification of the offending drug. The second step is its removal. Often this action is all that is needed. Mild symptoms will disappear without treatment in a few days or weeks after a patient stops taking the drug. Severe skin reactions require local or systemic treatment. Local treatment includes soothing baths, lotions, and steroid creams. (However, creams containing methylparabens should be used with caution, for such creams may themselves provoke contact dermatitis.) If secondary bacterial infections develop, antibiotics may be used unless a patient has shown an allergic reaction to a specific antibiotic. For severe systemic reactions, fluids or diuretics may help to eliminate the drug from the body and hasten recovery. Life-threatening anaphylactic reactions require the prompt use of epinephrine (Adrenalin), assurance that the airway passages are open, and administration of oxygen and intravenous fluids.

When reactions to a drug are similar to serum sickness, the symptoms usually disappear after the drug clears the body. Sometimes, however, antihistamines are given to control hives and aspirin is used to ease joint pain (if the patient is not sensitive to aspirin). Corticosteroids are used for severe symptoms of the skin and joints and for treatment of blood vessel inflammation and involvement of internal organs as a result of an allergic response.

Patients who are intolerant to insulin during the early stages of treatment of their diabetes usually are able to tolerate it with continued administration. In some cases, however, the allergy persists. The administration of antihistamines or corticosteroids or a change in the animal source and/or purity of the insulin may give relief. When other methods are not successful, severe systemic reactions to insulin can be treated by desensitization. The patient at first receives small doses, which are increased gradually under the supervision of a doctor as tolerance is achieved.

If skin tests show that the patient is actually allergic to the zinc component of the insulin preparation, zinc-free insulin is recommended. Purified human insulins manufactured by new procedures are undergoing clinical trials and are expected to be of great value in the treatment of diabetes and insulin allergy.

When prompt preventive treatment for tetanus is required by patients who have not previously been immunized for tetanus, human hyperimmune tetanus gamma globulin should be used rather than horse tetanus antitoxin. The best preventive treatment, however, is for the patient to maintain the active tetanus immunization with a booster injection once every 10 years.

Substances chemically related to an allergy-causing drug often produce similar adverse

reactions. In aspirin-sensitive people, however, drugs that are *not* chemically related to aspirin (such as tartrazine) may provoke similar reactions. Such reactions are not predictable.

Substitute medications are usually available for persons with sensitivity to a particular drug. Aspirin can be replaced by acetaminophen. Tests can be conducted to find which antibiotic other than penicillin is effective against a bacterial infection.

Subacute bacterial endocarditis, an infection of the inner lining of the heart, is perhaps one of the few infections that calls for immediate treatment with penicillin, even if the patient is allergic to this antibiotic. Such patients are desensitized by being given small doses of penicillin at frequent intervals, with the amount increased gradually until the therapeutic dose is tolerated. Of course, the patient is hospitalized during this treatment and a doctor is constantly in attendance, with all emergency measures available. Unfortunately the desensitization, which allows penicillin to be tolerated, may last only for the duration of the immediate treatment, and the allergy may return after a period of time.

The best way to prevent recurrence of allergic reactions to a drug is to avoid use of the drug. The patient should be aware of hidden sources of the drug, such as ingredients of over-the-counter medications. Treatment with several drugs in combination should be avoided if possible. Patients with asthma and nasal polyps should be very careful in their use of aspirin. The allergic patient should learn both the generic name and the trade name of the offending drug and should inform other doctors who will provide care in the future. A special identification card should be carried, or a Medic Alert* tag or bracelet should be worn in case of an accident.

*Medic Alert tags and bracelets can be ordered from the Medic Alert Foundation, Box 1009, Turlock, California 95380.

How can research help?

Although many of the body mechanisms involved in allergic reactions to drugs are now understood, many gaps in our knowledge of this field still exist. Further research should result in improved tests for diagnosing and even predicting allergies to specific drugs. Better methods need to be developed for preparing patients for treatment with the drugs to which they are allergic.

Throughout the United States, research supported by NIAID is helping scientists to study the various features of drug allergy in order to provide solutions to questions still unanswered.

Clinical testing of penicillin products is being coordinated currently at six university medical centers. The objective is to find out whether skin testing will predict immediate hypersensitivity reactions to penicillin. The patients are hospitalized adults who may or may not have a history of penicillin sensitivity but require treatment with penicillin. Penicillin itself and its breakdown products are used, and the tests are done very carefully. Testing begins with the prick test. A small needle is used to puncture the skin on which the test substance has been placed. If the patient has no reaction to the prick test, the intradermal test is used to inject tiny amounts of the penicillin antigen under the skin. If the intradermal test produces no reaction, a final small test dose is injected under the skin before the penicillin is administered at full-strength levels.

When the skin test results are positive and no other drug can be substituted for penicillin, the patient must undergo desensitization with small, frequent doses increased gradually to the therapeutic level.

Clinicians at The Johns Hopkins University School of Medicine are also gathering evidence that supports the value of skin testing to predict tolerance to penicillin. They report that patients whose skin tests are negative have fewer reactions than patients not tested. They confirm previous observations that when penicillin is injected into muscle, the numbers of allergic reactions are greater than when it is taken by mouth.

At Massachusetts General Hospital, NIAID-supported scientists are studying allergy to penicillin and cephalosporins (structurally similar antibiotics) to determine if cross-reactivity occurs in allergic patients. They are also studying whether certain types of drug rashes indicate permanent hypersensitivity to these antibiotics.

Investigations on reactions to contrast dyes used for certain X-ray tests are being carried out at the University of Michigan through funding by NIAID. Blood tests of people who develop chronic hives, angioedema, and even anaphylaxis-like reactions to contrast dyes may reveal whether a tendency for this allergic-like response can be predicted and what the body mechanisms may be.

Scientists at the NIAID Asthma and Allergic Disease Centers at the Scripps Institute in La Jolla, California, and at Northwestern University in Chicago, Illinois, have also been studying reactions to contrast dyes for several years. Both groups report that it is very difficult to predict who will have a tendency to react to contrast dyes. Skin tests have been shown to be poor indicators of both sensitivity and insensitivity. However, investigators at Northwestern University report that, for a special group of high-risk patients who have a medical need for these X-rays, the administration of antihistamines and prednisone before a sched-

uled X-ray significantly decreases the incidence and severity of the reactions.

The NIAID is presently funding a study of patients with insulin allergy at The Johns Hopkins University School of Medicine. Investigators there hope that observations on variations in the amounts of antibodies in patients who have been desensitized to insulin will shed light on the role of antibodies in acquiring tolerance to injections not only of insulin but also of other foreign proteins.

NIAID-supported researchers at the Scripps Institute have been successful in desensitizing aspirin-sensitive asthmatic patients by cautiously giving them small and then increasingly larger oral doses of this medication. Desensitization to aspirin may allow such patients to reduce or even discontinue their asthma medications such as corticosteroids.

What About the Future?

The need to be able to predict, diagnose, and treat drug allergies is obvious. Studies such as those described, in combination with general research that is continually expanding in the basic science of immunology, will hasten and improve our ability to handle the problems of drug allergy.

Because the array of drugs available to the physician is growing annually, new potential allergens will be continually encountered. After the tools and techniques for predicting, diagnosing, and treating drug allergy are developed by scientists, new drug problems can be more readily met as they emerge.

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